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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,482	12/12/2005	Frans Eduard Janssens	PRD2077USPCT1	3160

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EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
03/31/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,482	JANSSENS ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-14 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *9 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's submission filed December 7, 2009 has been received and entered into the present application.

Status of claims

The amendment filed on August 6, 2009 is acknowledged. Claims 2-8 and 15-20 have been canceled and claims 9 and 21-26 have been withdrawn. Claims 1 and 10-14 are under examination in the instant office action.

Applicants' arguments, filed on August 6, 2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Responses are limited to Applicants' arguments relevant to either reiterated or newly applied rejections.

Claim Objections

Claim 12-13 are objected because of the following informalities: typographical errors. The recitation, "and derivatives and pharmaceutical acceptable salts thereof" in line 6 of claim

12 should be corrected to --derivatives thereof or pharmaceutical acceptable salts thereof--. The recitation, "selected from the group consisting of ……., hydromorphone and pharmaceutical acceptable salts and derivatives thereof" in lines 3-4 of claim 13 should be corrected to -- selected from the group consisting of ……., and hydromorphone; pharmaceutical acceptable salts thereof, or derivatives thereof --.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is

whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims recite a generic genus, *i.e.*, generic derivatives of opioid analgesics.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

Applicants provide no description of the claimed derivatives of opioid analgesics, either in word, by structure, by formula, by chemical name, or by physical properties that would

indicate that Applicants were in possession of the claimed derivatives at the time of the invention. The Merriam-Webster's Collegiate Dictionary defines "derivative" as, "a chemical substance related structurally to another substance and theoretically derivable from it." Hence, one of ordinary skill in the art could not ascertain what compounds are encompassed by the claimed "derivatives". In addition, the specification does not disclose any examples of the claimed derivatives. Furthermore, Applicants do not describe the structural features of such derivatives that would possess the claimed activity.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All the dependent claims are included.

Claim 1 recites "a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, an opioid analgesic and (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide……; and pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof".

First, it is unclear what "thereof" is referring to. Does it refer to "a pharmaceutically acceptable carrier", "an opioid analgesic", or "(+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide".

Second, does the composition additionally comprise said "pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof" by using the transitional phrase "; and"? Or, is the claim 1 drawn to a pharmaceutical composition and "pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof"?

Third, there is a lack of antecedent basis for the limitations, "the stereochemically isomeric forms" and "the N-oxide form".

In view of the species election, the claim 1 is examined as a pharmaceutical composition comprising a pharmaceutically acceptable carrier, fentanyl, and (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1 and 10-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent 5,880,132 (issue date: 3/9/1999) in view of US patent 6,197,772 B1.

US patent 5,880,132 teaches a pharmaceutical composition comprising a tachykinin antagonist in paricular an NK_1 receptor antagonist and an opioid analgesic, together with at least one pharmaceutically acceptable carrier or excipient for the treatment or prevention of pain or nociception (abstract; column 1, lines 7-10; and column 2, lines 33-36). US patent 5,880,132 defines that the term opioid is generally accepted to refer in a generic sense to all drugs, natural or systhetic with morphone-like action and lists fentanyl as a preferred opioid analgesic (column 1, line 52-56, column 26, lines 23-29, claim 2). US patent 5,880,132 further teaches that the composition may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of pain and formulated into unit dosage forms for oral administration (column 2, lines 42-46, column 26, line 56-60, and claim 4). This teaching reads on the limitations recited in instant claims 11 and 14. In addition, the reference teaches that

respiratory depression is a common side effect associated with opioid analgesic usage (column 2, lines 1-5) and that the composition is possible to treat pain with a sub-maximal dose of an opioid analgesic thereby reducing the likelihood of side-effects associated with opioid analgesic usage such as respiratory depression by the use of a combination of a tachykinin antagonist and an opoid analgesic (column 2, line 61-column 3, line 3). Furthermore, it teaches that the tachykinin antagonists of use may be any tachykinin antagonist known from the art and preferably, the tachykinin antagonist is an NK-1 or NK-2 receptor antagonist, especially an NK-1 receptor antagonist (column 3, lines 7-10).

The reference differs from the instant claims insofar as it does not teach the elected species, (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N-(2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid.

US patent 6,197,772 B1 teaches (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as tachykinin antagonist (NK_1 receptor antagonist) (column 1, lines 9-14, column 1, line 44-column 4, line 23; column 7, line 39-column 8, line 5; claims 1-3), which can be used for the treatment of pain, emesis, or asthma (column 18, lines 33-44). Also, US patent 6,197,772 B1 teaches that the compound may be formulated into various pharmaceutical forms for administration purposes such as oral administration (column 18, line 45-56). In addition, it discloses that an effective therapeutic daily amount is from about 0.001 mg/kg to about 40 mg/kg body weight, more preferably from about 0.01 mg/kg to about 5 mg/kg body weight, wherein the disclosed dosage range is identical to the dosage range used for reducing respiratory depression in the instant specification (p18, line 9-12 and p54, example C4). Thus, the effective therapeutic daily amount

of (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic taught by US patent 6,197,772 B1 reads on "an amount effective to reduce the respiratory depression caused by the administration of an opioid analgesic" recited in the instant claim 1 .

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the compound of US patent 6,197,772 B1 for the combination with fentanyl as taught by US patent 5,880,132 in the treatment of pain since US patent 6,197,772 B1 teaches (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N-(2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as tachykinin antagonist and US patent 5,880,132 already suggests that any tachykinin antagonist known from the art can be used for the combination with an opioid analgesic, wherein the combination is beneficial for reducing opioid analgesic-associated side-effects such as respiratory depression. Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute one tachykinin antagonist with another tachykinin antagonist for the combination with an opioid analgesic as taught by US patent 5,880,132 since the skilled artisan would have been able to carry out such a substitution and the results (i.e., treating pain while reducing opioid analgesic-associated side-effects such as respiratory depression) were reasonably predictable. Furthermore, one of ordinary skill in the art at the time the invention was made would have reasoned to use an effective amount of (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N-(2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as taught by US patent 6,197,772 B1 for making a combination with an opioid analgesic as taught by US patent 5,880,132. When the disclosed effective amount of (+)-(B)-

trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid is used in combination with an opioid analgesic as taught by US patent 5,880,132, reducing respiratory depression would be an expected outcome. It is noted that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Response to Applicants' arguments:

Applicants argued that neither Hill or Janssens *et al.* suggest or disclose that (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid can reduce respiratory depression caused by an opioid analgesic. However, the argument is not deemed to be persuasive. As stated above, US patent 5,880,132 already teaches that the use of a combination of a tachykinin antagonist with an opoid analgesic can treat pain with a sub-maximal dose of an opioid analgesic while reducing the likelihood of side-effects associated with opioid analgesic usage such as respiratory depression and suggests that any tachykinin antagonist known from the art can be used for the combination. Furthermore, US patent 6,197,772 B1 teaches the same compound and the same effective therapeutic daily amount as the instant invention as stated above, thus when the effective amount of (+)-(B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as taught by US patent 6,197,772 B1 is used in combination with an opioid analgesic as taught by US patent

5,880,132, reducing respiratory depression would be an expected outcome. It is noted that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00-6:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-071818. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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